REMARKS

Claims 11-13, 18-21, 30-31, 40-48, 51-52, and 75-90 are pending in this application.

Claims 1-10, 25-29, 38-39, and 56, were previously canceled without prejudice or disclaimer. Claims 14-17, 22-24, 32-37, 49-50, 53-55, 57-74, 77-78, 81-82, 86-87 and 89-90 have been withdrawn from consideration as being drawn to a non-elected invention.

Regarding Applicants claim for priority, attached hereto is an English language translation of PCT/JP0204084.

In view of the remarks set forth herein, further and favorable consideration is respectfully requested.

I. At page 3, item 3, of the Official Action, the Examiner objects to claims 11-13, 30, 31, and 40-48 under 37 CFR 1.75(c) as being in improper form because they are directly or indirectly dependent form subsequent claims.

In view of the following, this objection is respectfully traversed.

Applicants note that MPEP § 608.01(n) IF, directed to dependent claims, recites in part the following:

> "However, in situations where a claim refers to a numerically following claim and the dependency is clear, both as presented and as it will be renumbered at issue, all claims should be examined on the merits and no objection as to form need be made. In such cases, the examiner will renumber the claims into proper order at the time the application is allowed. (See Example B, below.)"

Accordingly, it is submitted that this objection is improper and should be withdrawn.

II. At page 3, item 4, of the Official Action, the Examiner states that the priority date for the instant application is still considered to be October 27, 2003.

In view of the following, Applicant's assert that the priority date of the instant application is April 24, 2001.

Applicant's assert that the translation of the certified copy of the priority document submitted on April 13, 2007 is true and accurate in accordance with 37 CFR § 1.55.

In view of the foregoing statement, Applicant's assert that the priority date of the instant application is April 24, 2001.

III. At page 6, item 13, of the Official Action, claims 11-13, 18-21, 30, 31, 40-48, 51, 52, 75-76, 79-80, 83-85, and 88 have been rejected under 35 USC § 103, as being unpatentable over Ramiya et al., in view of each of Serup, Oberg-Welsh et al., and Suzuki et al.

The Examiner asserts that it would have been obvious to the skilled artisan to use antibodies directed against c-Met and additional markers, to separate the pancreatic stem cells from the single cell suspension of Ramiya et al with the motivation to separate provided by Serup, Oberg-Welsh et al., and Suzuki et al.

In view of the following, this rejection is respectfully traversed.

The U.S. Supreme Court in *Graham v. John Deere Co.*, 148 U.S.P.Q. 459 (1966) held that non-obviousness was determined under § 103 by (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and, (4) inquiring as to any objective evidence of

nonobviousness.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, Slip Opinion No. 04–1350, 550 U. S. ____ (April 30, 2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, *supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

With regard to motivation to combine references, **MPEP 2143** discusses the requirements of a *prima facie* case of obviousness. First, there must be some suggestion or motivation to combine the reference teachings or to modify the reference, and second, there must be a reasonable expectation of success. Finally, the prior art reference or references when properly combined, must teach or suggest all the claim limitations.

Regarding motivation to modify properly combined references, **MPEP 2143.01** states that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there is no suggestion or motivation to make the proposed modification. Further, the proposed modification cannot change the principle operation of a reference.

Regarding *teaching away*, **MPEP 2141.02** states that prior art must be considered in its entirety, including disclosures that *teach away* from the claims. See also **MPEP 2145(X)(D)**. The Federal Circuit in *Takeda v. Alphapharm* found that the prior art taught away from the closest compound because the prior art in fact disclosed a broad selection of compounds where the closest prior art compound exhibited negative properties that would have led the skilled artisan away from that compound.

In *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.,* Federal Circuit, No. 06-1325 (June 28, 2007), the Federal Circuit rejected Alphapharm's argument that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound most promising to modify in order to improve its antidiabetic activity and thus potentially arrive at the claimed pioglitazone.

The district court considered three references in reaching its determination, namely Takeda's '200 patent; Sodha II; and Takeda's '779 patent. The district court found that Sodha II taught away from compound b and that any suggestion in the '779 patent to select compound b was essentially negated by the disclosure of Sodha II in view of the more exhaustive and reliable scientific analysis presented by Sodha II and the teaching away. Accordingly, the Federal Circuit accorded more weight to the Sodha II reference.

Present claim 75 recites a method of separating a pancreatic stem cell from the pancreas of a mammal, comprising isolating pancreatic cells from the pancreas of a mammal to produce pancreatic cells; contacting the pancreatic cells with at least four antibodies or functional fragments thereof each having specific affinity a different marker protein selected from the group consisting of c-Met, c-Kit, CD45, and TER119; and separating the pancreatic stem cells from the pancreatic cells based on antibody binding between the antibodies and the marker proteins to produce separated cells.

Present claim 76 recites a method of separating a pancreatic stem cell from the pancreas of a mammal, comprising isolating pancreatic cells from the pancreas of a mammal to produce pancreatic cells; contacting the pancreatic cells with at least five antibodies or functional fragments thereof each having specific affinity for a different marker protein selected from the group consisting of c-Met, c-Kit, CD45, TER119, and Flk-1; and separating the pancreatic stem cells from the pancreatic cells based on antibody binding between the antibodies and the marker proteins to produce separated cells.

Present claims 11-13, 30-31, 40-48, and 79-80, 83-85, and 88 are directly or indirectly dependent on independent claim 75 or 76.

Present claim 18 recites a cloned pluripotent pancreatic stem cell, that shows c-Met$^+$, c-Kit$^-$, CD45$^-$ and TER119$^-$. Present claim 19 recites a cloned pluripotent pancreatic stem cell, that shows c-Met$^+$, c-Kit$^-$, CD45$^-$, TER119$^-$ and Flk-1$^-$.

Present claims 20-21 are dependent on independent claim 18. Claims 51-52 are dependent on independent claim 19.

In view of the following, it is submitted that a *prima facie* case of obviousness has not been established.

Ramiya et al. describes the *in vitro* growth of islets from stem cells where adult islet ductal structures were isolated and cultured. Gene expression was then detected by RT-PCR. Ramiya et al. describe at page 279 that transcripts for insulin I, insulin II, insulin receptor, and hepatocyte growth factor and its receptor c-Met, were detected. The Examiner states at page 13 of the Official Action that "Ramiya et al. do not teach separating or identifying the pancreatic stem cells by using antibodies against c-Met, c-Kit, CD45, TER119, and Flk-1."

Serup describes that the identification of reliable surface markers of pancreatic stem cells is a priority. Serup also states that "***Unfortunately, there are no reliable surface markers for pancreatic stem cells; indeed, their very identity has been obscure***...some data indicate an emerging profile. A candidate pancreatic stem cell, which is characterized by its expression of the neural stem-cell marker nestin and lack of ... islet- and duct-cell markers, was

described...." Serup concludes that there are plenty of obstacles that must be overcome before a viable stem cell based therapy for diabetes is in hand and that there is a need to better understand the development of the endocrine pancreas and stem cells.

Oberg-Welsh et al. describes the expression of protein tyrosine kinases in insulin producing cells and immunoreactivity for the receptor Flk-1. Other receptors identified were the FGFR-4, the IGF-1 receptor, c-Kit and the cytoplasmic tyrosine kinase Jak2. Oberg-Welsh et al. also describes that Trk-A (tyrosine kinase receptor) is expressed in fetal islets.

Suzuki et al. describes flow-cytometric separation and enrichment of hepatic progenitor cells in the developing mouse liver.

It is submitted that a *prima facie* case of obviousness has not been established because (i) there is no motivation supporting the combination of Suzuki et al. with any of Ramiya et al., Serup, and Oberg-Welsh et al. taken alone or together; and (ii) nothing in any of Ramiya et al., Serup, Oberg-Welsh et al., and Suzuki et al., taken alone or together, teach or suggest all of the limitations of the present claims as required by *Amgen* and *In re Wilson*.

There is no motivation supporting the combination of Suzuki et al. with any of Ramiya et al., Serup, and Oberg-Welsh et al., because Suzuki et al. is concerned with hepatic cells while the remaining references are concerned with pancreatic cells. The skilled artisan reviewing any of Ramiya et al., Serup, and Oberg-Welsh et al. that are concerned with pancreatic cells would have no motivation to look to Suzuki et al. that is concerned with hepatic cells. Likewise,

the skilled artisan reviewing Suzuki et al. that is concerned with hepatic cells, would have no motivation to look to any of Ramiya et al., Serup, and Oberg-Welsh et al. that are concerned with pancreatic cells.

Assuming *arguendo*, the combination of Suzuki et al. with Ramiya et al., Serup, and Oberg-Welsh et al. proper, it is submitted that nothing in any of Ramiya et al., Serup, Oberg-Welsh et al., and Suzuki et al., taken alone or together, teach or suggest all of the limitations of the present claims as required by *Amgen* and *In re Wilson*.

Claim 75 recites the step of contacting the pancreatic cells with at least four antibodies and/or functional fragments thereof each having specific affinity a different marker protein selected from the group consisting of c-Met, c-Kit, CD45, and TER119. Claim 76 recites the step of contacting the pancreatic cells with at least five antibodies and/or functional fragments thereof each having specific affinity for a different marker protein selected from the group consisting of c-Met, c-Kit, CD45, TER119, and Flk-1.

None of the references teach or suggest contacting pancreatic cells with at least four antibodies and/or functional fragments thereof each having specific affinity for a different marker protein selected from the group consisting of c-Met, c-Kit, CD45, and TER119 as required by claim 75 and claims dependent therefrom, or contacting pancreatic cells with at least five antibodies and/or functional fragments thereof each having specific affinity a different marker protein selected from the group consisting of c-Met, c-Kit, CD45, and Flk-1 as required by claim 76 and claims dependent therefrom.

Ramiya et al. describes, at page 279, determining the expression of islet cell-associated markers by islet-producing stem cells (IPSCs) and islet progenitor cells (IPCs) by detecting transcripts for insulin I, insulin II, insulin receptor, hepatocyte growth factor and its receptor C-MET, glucagon, somatostatin, glucose transporter-2 receptor, glutamic acid decarboxylase-67, insulin-like growth factor-I, and insulin-like growth factor-II. Ramiya et al. also describes, at page 279, analyzing the expression of genes including regenerating gene-1, PDX-1, β-galactosidase, tyrosine hydroxylase, beta2/neuroD, paired box genes 4 and 6, insulin-related protein 1, and Nkx6.1, from IPSCs and IPCs. From the foregoing, it can be seen that Ramiya et al. describes at least 20 factors. Ramiya et al. does not provide any motivation or suggestion to select C-MET from the 20 described factors.

Serup describes that pancreatic stem cells express the neural stem-cell marker nestin. Serup also recites that there is a ***lack of established islet and duct-cell markers***. At most, Ramiya et al. in view of Serup, ***suggest nothing more than trying all 21 factors*** in an attempt to establish islet-cell and duct-cell markers.

Oberg-Welsh et al. describes the receptor Flk-1, FGFR-4, the IGF-1 receptor, c-Kit, the cytoplasmic tyrosine kinase Jak2, and Trk-A. Oberg-Welsh et al. does not provide any motivation or suggestion to select c-Kit from the six described factors, let alone combine it with one factor (C-Met) out of the 20 described by Ramiya et al. At most, Ramiya et al. in view of Serup and Oberg-Welsh et al., ***suggest nothing more than trying all 27 factors*** in an attempt to

establish islet-cell and duct-cell markers.

Suzuki et al. describes flow-cytometric separation and enrichment of hepatic progenitor cells in the developing mouse liver, and describes that hematopoietic stem cells were excluded by gating out $CD45^+$ and $TER119^+$. Suzuki et al. ***does not teach or suggest any pancreatic islet-cell or duct-cell marker.***

The fact that a claimed species or subgenus is encompassed by a prior art genus ***is not sufficient*** by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."); *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992). A proper obviousness analysis requires consideration of "whether the prior art would also have revealed that in so making or carrying out [the claimed invention], those of ordinary skill would have a reasonable expectation of success."); *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). A finding of obviousness requires that some motivation to select the claimed species or subgenus must be taught by the prior art. See, e.g., *Deuel*, 51 F.3d at 1558-59, 34 USPQ2d at 1215

In the present case, none of the applied references, taken alone or together, suggest selecting the claimed markers. Further, none of the references taken alone or together, provide a reasonable expectation of success. In fact, ***Serup expressly states that "Unfortunately, there are no reliable surface markers for pancreatic stem cells; indeed, their very identity has been***

obscure..." and that "***there are plenty of obstacles that must be overcome before a viable stem cell based therapy for diabetes is in hand***...It underscored the need to better understand the development of the endocrine pancreas and stem cells."

In conclusion, at most, Ramiya et al. in view of Serup, Oberg-Welsh et al., and Suzuki et al., taken alone or together, ***suggest nothing more than trying all 27 factors in an attempt to establish islet-cell and duct-cell markers***.

"Obvious to try" is not the proper standard for patentability. In fact, the *KSR* court held that for something to be obvious as being "obvious to try" there must be a finite number of identified, predictable solutions. In the present case, Serup teaches that there are ***no reliable surface markers***. Further, biotechnology is considered a somewhat unpredictable art as compared, for example, to mechanical engineering. Accordingly, in the present case, the art itself teaches that there are ***no predictable solutions***. Therefore, it is submitted that the present claims are unobvious over the combination of applied references.

In addition, as discussed above, the Federal Circuit in *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.,* rejected Alphapharm's argument that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound most promising to modify in order to improve its antidiabetic activity and thus potentially arrive at the claimed pioglitazone. The district court considered three references in reaching its determination, namely Takeda's '200 patent; Sodha II; and Takeda's '779 patent. The district court found that Sodha II

taught away from compound b and that any suggestion in the '779 patent to select compound b was essentially negated by the disclosure of Sodha II.

With regard to the combination of Ramiya et al., Serup, Oberg-Welsh et al., and Suzuki et al., Serup ***teaches away*** from the selection of ***any*** specific surface markers for pancreatic stem cells because Serup teaches that ***none*** of the markers ***are reliable surface markers***.

In view of the foregoing, it is submitted that nothing in Ramiya et al., Serup, Oberg-Welsh et al., and Suzuki et al., taken alone or together, suggest the presently claimed subject matter within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

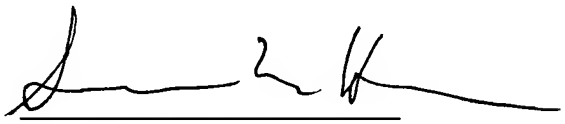
CONCLUSION

In view of the foregoing, Applicant submits that the pending claims are in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicant petitions for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP



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